The Latest in HIV Vaccine Development

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The views expressed are those of the presenter and should not be construed to represent the positions of the U.S. Army or DoD

HIV Vaccine Development

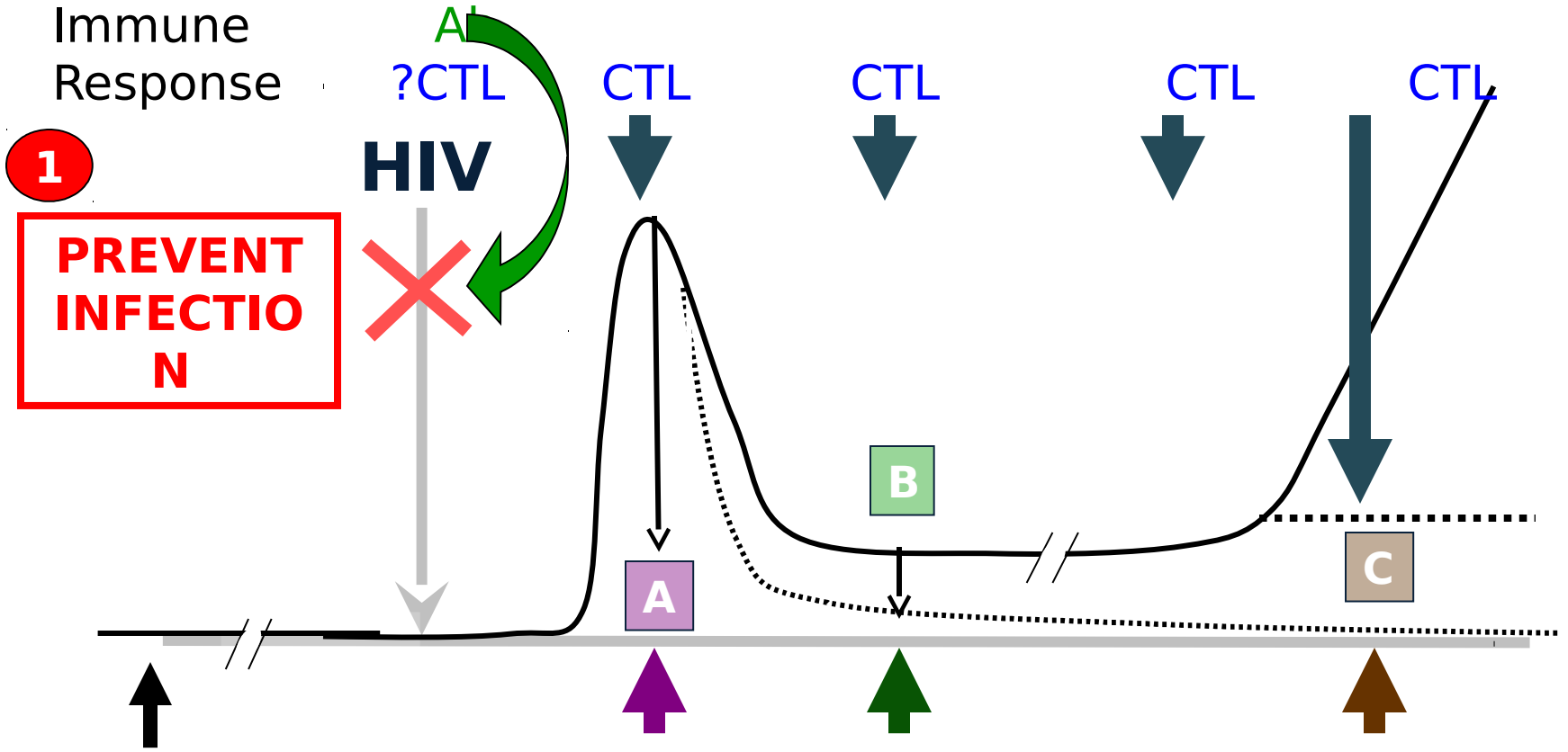
- Why is it difficult to develop an HIV vaccine?
- RV144: Thai Phase III HIV Vaccine Trial
- RV144: Immune correlates
- RV144 V2 Sieve Analysis
- What is next for Pox Protein Prime Boost?
- The Global Vaccine
- The promise of broadly neutralizing antibody?
- Early Phase Trials

Why is it difficult to develop an HIV vaccine?

HIV is not like viruses that make the“classic” vaccines like polio or hepatitis A?

- Classic vaccine – disease model
  - Variable courses and sequelae but almost all recover completely (polio, rubella, influenza)
  - Vaccine induced immune response or natural immune response clear virus completely
  - Lifelong immunity from reinfection (or after booster immunization)
- HIV
  - Disease progressive, no spontaneous recovery or “cures”
  - Virus is never cleared or eradicated
  - Infection does not prevent reinfection (superinfection)

How might an HIV/AIDS vaccine work?



A. Lower Initial Peak of Viremia

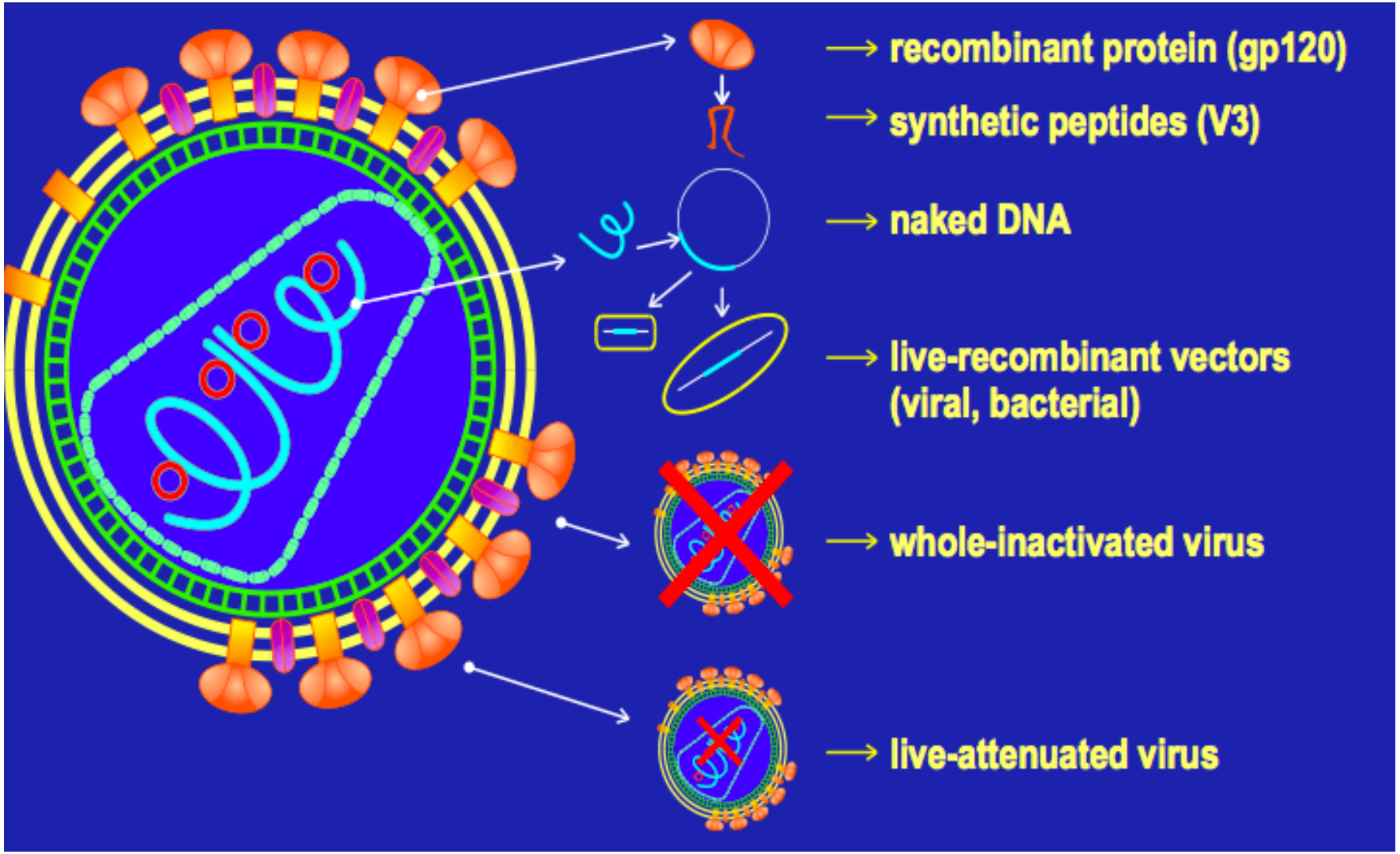
B. Decrease viral set point

C. Delay Progression

Why is it so hard to develop a vaccine against HIV?

- HIV is highly variable: RT, subtypes, recombination, swarm
- HIV-1 fools the immune system by using decoys, camouflage, hides its weak points, and has proteins that decrease antiviral responses
- HIV becomes integrates itself into long-lived memory cells and monocyte/macrophages – establishing pools of latently infected cells
- The HIV targets the coordinating center of the immune system – CD4 T helper cells

HIV vaccine approaches



Summary of HIV-1 Vaccine Efficacy Trials

Study protocol	Candidate vaccine	Phase	Sample size	Population enrolled	Location	Result	References
HVTN 505	DNA (VRC-HIVDNA016-00-VP) and rAd5 (VRC-HIVADV014-00-VP) (A, B, and C)	IIb	2494 in MITT analysis	Circumcised MSM and TG Ad5 Ab negative	USA	Stopped for futility. No efficacy on HIV acquisition and on plasma viral load	www.niaid.nih.gov/news/QA/Pages/HVTN505qa2013.aspx
RV144	ALVAC-HIV vCP1521 and AIDSVAX B/E (MN and CRF01_AE CM244) rgp120 in alum	III	16 403	Community	Thailand	31.2% efficacy against HIV-1 acquisition. No effect on plasma viral load	[19,94**,97,98*,99**,100,101,102**,103,104*,105,106]
HVTN 502: Step trial	MRKAd5 HIV-1 gag/pol/nef B	IIb	3000	MSM, high-risk heterosexual men and women	North and South America, Australia, Caribbean	No efficacy; transiently increased infection risk; Stopped	[88–90,107**,108,109]
HVTN 503 Phambili trial	MRKAd5 HIV-1 gag/pol/nef B	IIb	3000; 801 enrolled	Heterosexual men and women	South Africa	No efficacy – Stopped follow-up analysis suggests increased rate of HIV infection in vaccine recipient	[111,112]
Vax003	AIDSVAX B/E gp120 (MN and CRF01_AE CM244) gp120 in alum	III	2500	IDUs	Thailand	No efficacy	[113]
Vax004	AIDSVAX B/B gp120 (MN and GNE8) gp120 in alum	III	5400	MSM, high-risk women	USA	No efficacy	[114–120]

ALVAC-HIV (vCP1521), recombinant canarypox vector expressing Gag and Protease subtype B (LAI) and env gp120 CRF01_AE (TH023) linked to the transmembrane-anchoring portion of subtype B gp41 (LAI) genes; Ad5: Replication-defective recombinant Adenovirus 5-vectored vaccine; Ad5 Ab; Ad5-specific neutralizing antibody; VRC-HIVDNA016-00-VP, DNA plasmids expressing Gag, Pol and Nef subtype B (strains HXB2, NL4-3, NY5/BRU, respectively) and HIV-1 Env subtype A (strain 92rw020), B (strains HXB2/BaL) and C (strain 97ZA012); VRC-HIVADV014-00-VP, mixture of four rAd5 vectors encoding the HIV-1 Gag-Pol polyprotein subtype B (strains HXB2-NL4-3) and Env A, B and C matching the DNA Env components; TG, male-to-female transgender persons who have sex with men; MITT, modified intent-to-treat analysis.

From Excler JL, et al. Current Opin HIV AIDS, in press.

RV144: Thai Phase III HIV Vaccine Trial

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Trial Scrapbook: Infrastructure

Vaccine Distribution Center (VDC)

Health Center

Klaeng District Hospital

Clinical Site 200: Si Racha

Trial Registry and Repository Center

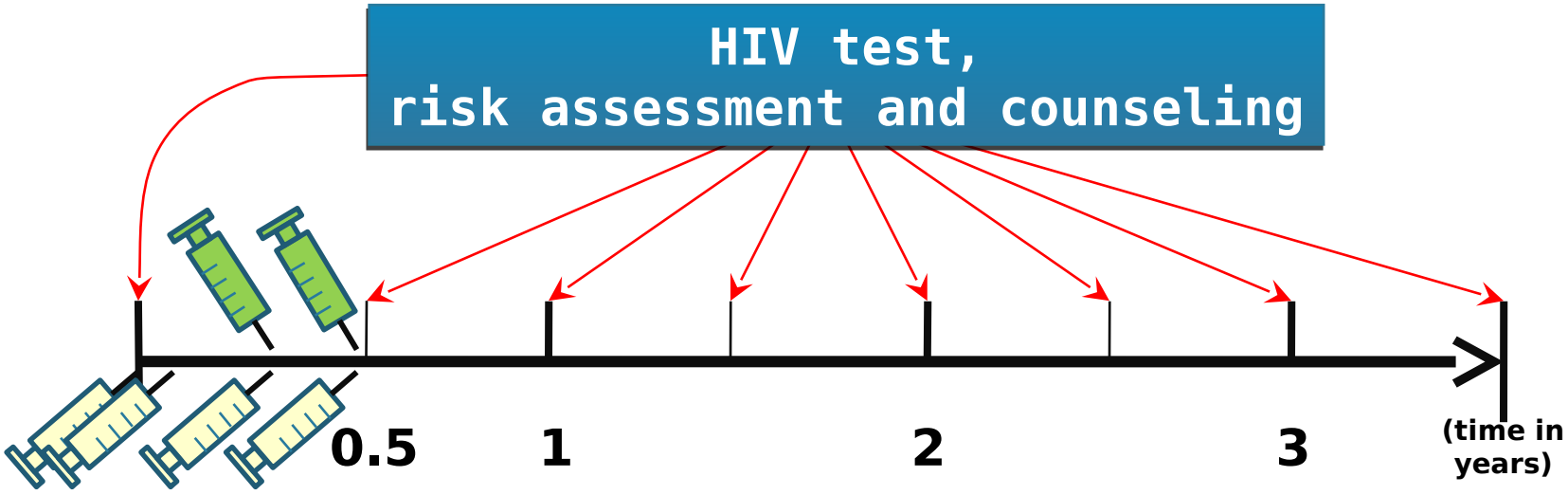
AFRIMS HIV Lab

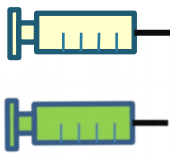
RV144 Trial: Key Dates and Statistics

- Screening started: *24 Sep 2003*
- First vaccination: *20 Oct 2003*
- Enrollment completed: *30 Dec 2005*
  - 60,000+ interested people
  - 26,675 volunteers screened
  - 16,402 volunteers enrolled
  - 16,395 rec'd at least one dose (mITT)
- Enrollment completed: *30 Dec 2005*
- Vaccination completed: *31 Jul 2006*
- Interim Analysis (mITT): *18 Jul 2007*
- 2007 – 2009: Roadmaps and Access, and Dossiers
  - *Commitment to ensuring the study participants would be first to learn of outcome regardless of result*
  - *Presented to WHO VAC*
- Final Analysis Meeting: *10-11 Sep 2009*
- Announcement: *24 Sep 2009*
- Presentation: *20 Oct 2009*
- Other statistics
  - 52,985 mITT p-y of follow-up (final)
  - 102,069 HIV EIA screening tests
  - 104,900 vaccine vials shipped, 100% accountability
  - 296,307 visits (final)
  - 641,157 specimens (plasma and cells, final)
  - 1,163,267 CRF pages (final)

Study Design, Vaccination and Follow-up Schedule

- Community-based, randomized, double-blind, placebo-controlled trial (V:P 1:1)
- Volunteers: HIV negative, 18-30 years of age
- Excluded: chronic disease, pregnancy or breastfeeding

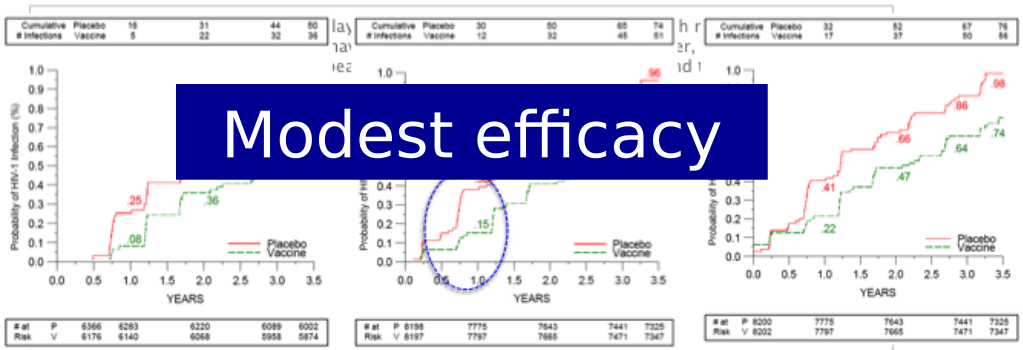




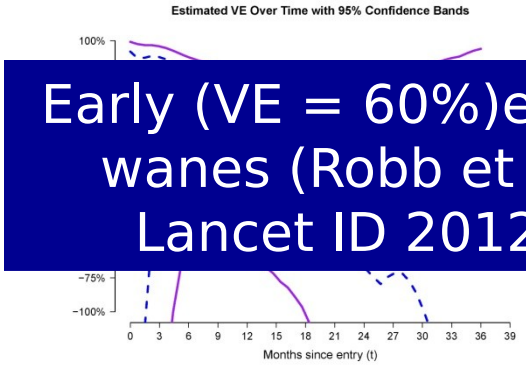
ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24

AIDSVAX® B/E gp120 boosting at week 12, 24

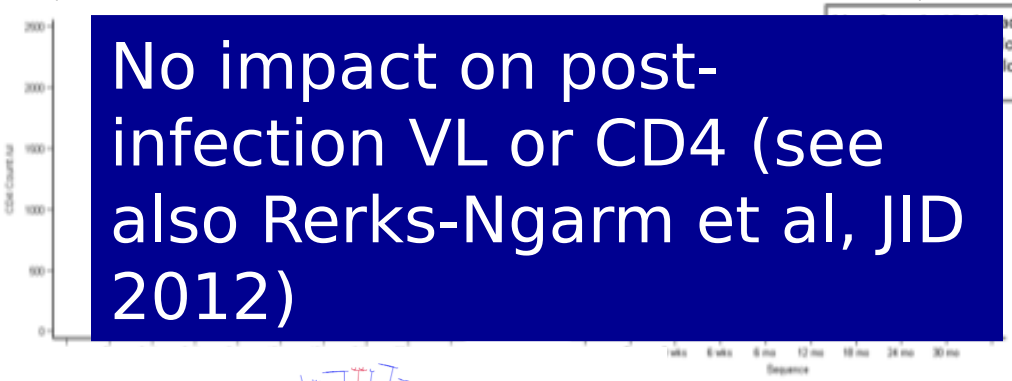
RV144 Summary



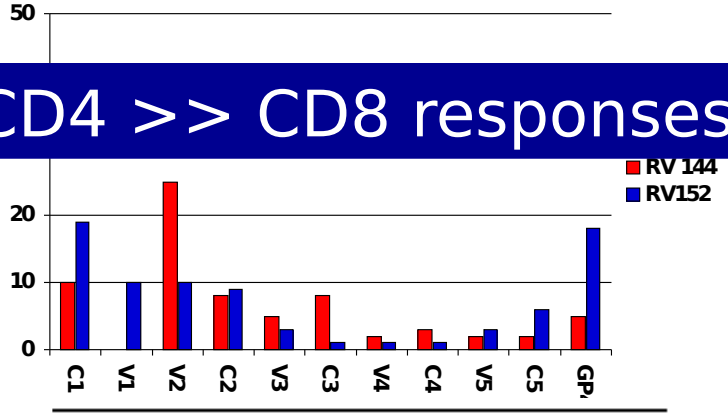
Modest efficacy



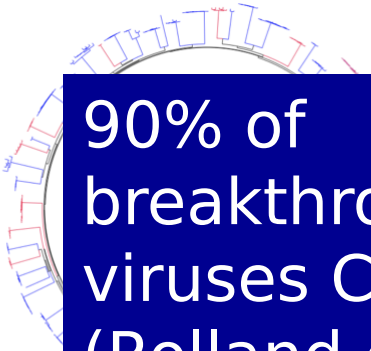
Early (VE = 60%)effect wanes (Robb et al, Lancet ID 2012)



No impact on post-infection VL or CD4 (see also Rerks-Ngarm et al, JID 2012)



CD4 >> CD8 responses



90% of breakthrough viruses CRF01_AE (Rolland et al, Nature, 2012)

bAb decreases rapidly

	(99% responders)	(99% responders)
E gp120	14558 (200-204800) (99% responders)	1000 (100-12800)* (99% responders)
B p24	205 (100-1600) (52% responders)	149 (100-200)* (18% responders)

P<0.0001 compared to placebo group - all Antigens
*: P<0.001 compared to 2 week time-point

Dr. Mark de Souza

RV144: Immune correlates or what did the vaccine do to decrease infection?

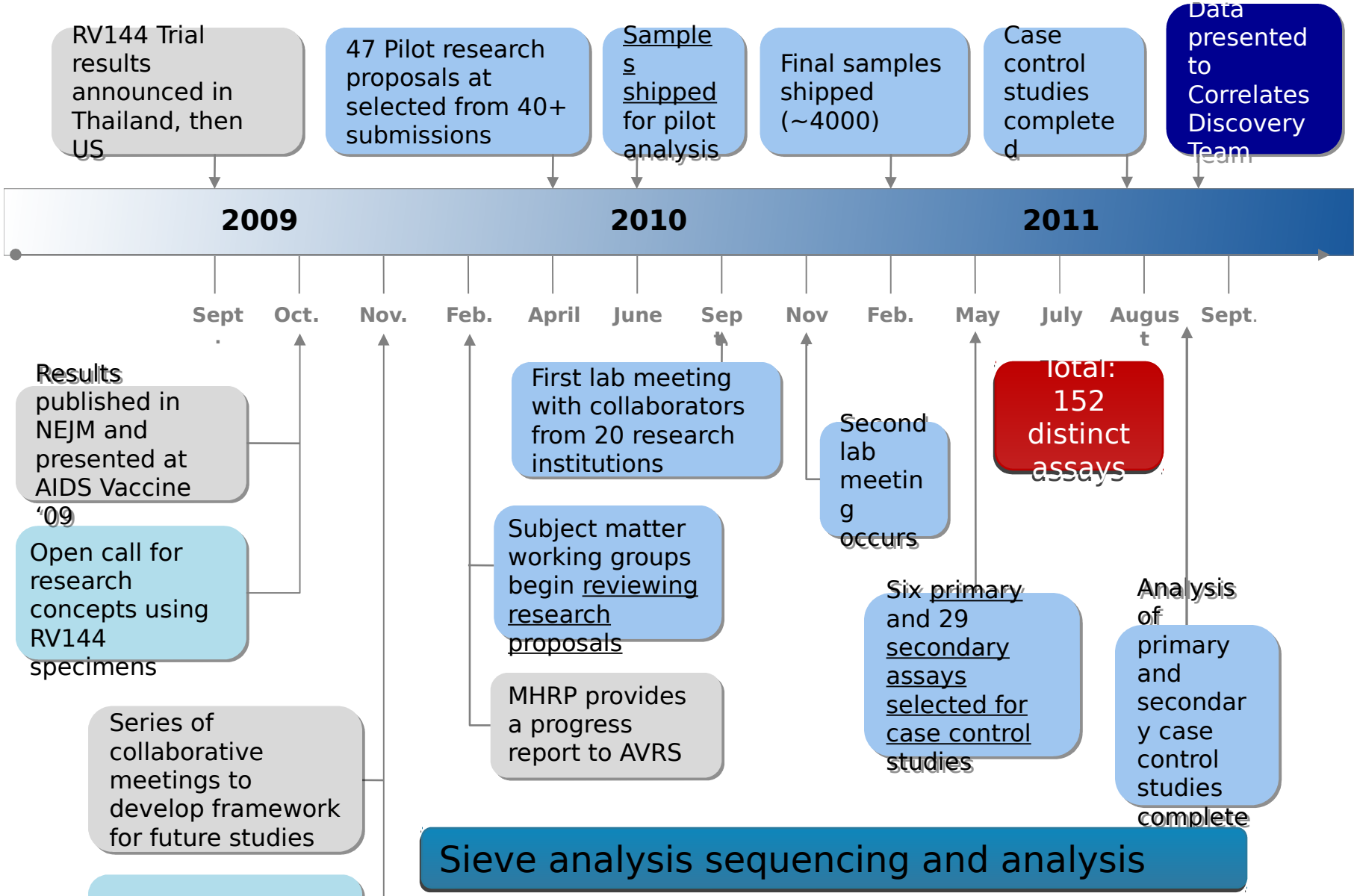
A Correlates Framework

Correlate	Definition
Correlate of Risk	An immunological measurement that correlates with the rate or level of a study endpoint used to measure vaccine efficacy in a defined population
Correlate of Protection	An immune marker statistically correlated with vaccine efficacy (equivalently, predictive of vaccine efficacy) that may or may not be a mechanistic causal agent of protection

A correlate is a laboratory test that provides a signal that the vaccine is working.

- Makes it easier (faster) to find <u>better</u> vaccines that have higher levels of the marker, for greater periods of time
- May lead to the development of a better animal model

Plotkin and Gilbert, CID, 2012; Qin et al, JID, 2007



TIMELINE FOR CORRELATES CASE-CONTROL ANA

Immunological Correlates

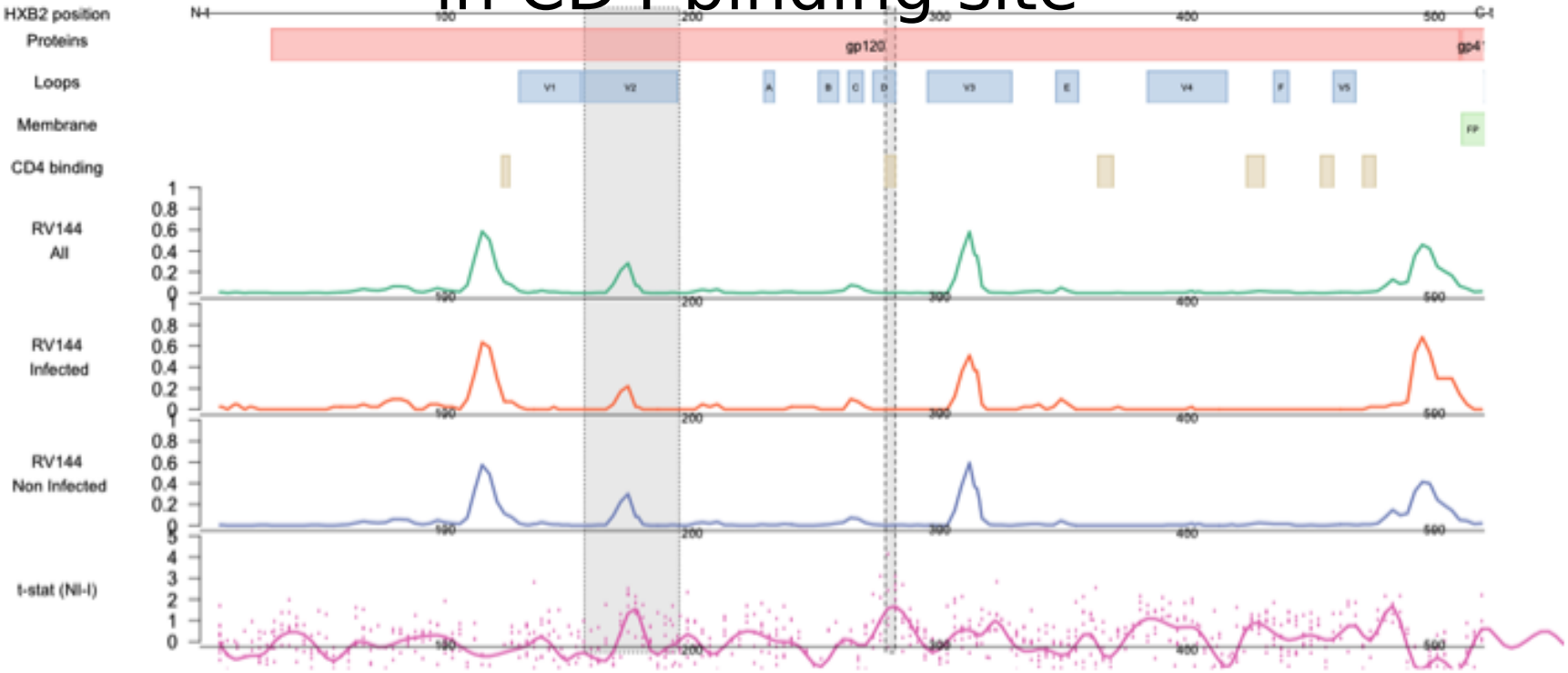
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2012 VOL. 366 NO. 14

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

Barton F. Haynes, M.D., Peter B. Gilbert, Ph.D., M. Juliana McElrath, M.D., Ph.D., Susan Zolla-Pazner, Ph.D., Georgia D. Tomaras, Ph.D., S. Munir Alam, Ph.D., David T. Evans, Ph.D., David C. Montefiori, Ph.D., Chitraporn Karnasuta, Ph.D., Ruengpueng Sutthent, M.D., Ph.D., Hua-Xin Liao, M.D., Ph.D., Anthony L. DeVico, Ph.D., George K. Lewis, Ph.D., Constance Williams, B.S., Abraham Pinter, Ph.D., Youyi Fong, Ph.D., Holly Janes, Ph.D., Allan DeCamp, M.S., Yunda Huang, Ph.D., Mangala Rao, Ph.D., Erik Billings, Ph.D., Nicos Karasavvas, Ph.D., Merlin L. Robb, M.D., Viseth Ngauy, M.D., Mark S. de Souza, Ph.D., Robert Paris, M.D., Guido Ferrari, M.D., Robert T. Bailer, Ph.D., Kelly A. Soderberg, Ph.D., Charla Andrews, Sc.M., Phillip W. Berman, Ph.D., Nicole Frahm, Ph.D., Stephen C. De Rosa, M.D., Michael D. Alpert, Ph.D., Nicole L. Yates, Ph.D., Xiaoying Shen, Ph.D., Richard A. Koup, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Jaranit Kaewkungwal, Ph.D., Sorachai Nitayaphan, M.D., Ph.D., Supachai Rerks-Ngarm, M.D., Nelson L. Michael, M.D., Ph.D., and Jerome H. Kim, M.D.

Case control analysis of microarray shows trend to inverse correlation at tip of V2 and in CD4 binding site



- Trend of inverse correlation for V2 peptides 54, 55 [starting at positions 166 and 169]
  - Peptide 555 [169-184] = Crown of V2 loop VQKEYALFYKLDVVP
  - Karasavvas et al. describe the vaccine's V2-crown directed antibody responses
- Trend of inverse correlation for the CD4 binding site peptides 89-90, despite low response rates
  - Among the contact sites for the most potent broadly neutralizing antibodies (e.g., VRC01, VRC03, etc.)

Multivariate Logistic Regression: Quantitative Variables RV144 Correlates (Haynes et al, NEJM 2012)

Variable	Relative risk	P-value	Q-value
IgA Binding to Envelope Panel	**1.54**	**0.027**	**0.08**
IgG Avidity A244 gp120	**0.81**	**0.37**	**0.56**
ADCC AE.HIV-1 Infected CD4 Cells	**0.92**	**0.68**	**0.68**
Tier 1 Neutralizing Antibodies	**1.37**	**0.22**	**0.45**
IgG Binding to gp70-V1V2	**0.57**	**0.015**	**0.08**
CD4+ T Cell Intracellular Cytokines	**1.09**	**0.61**	**0.68**

Case control study: 40 HIV+ vaccinees, 205 HIV- vaccinees; 40 placebo

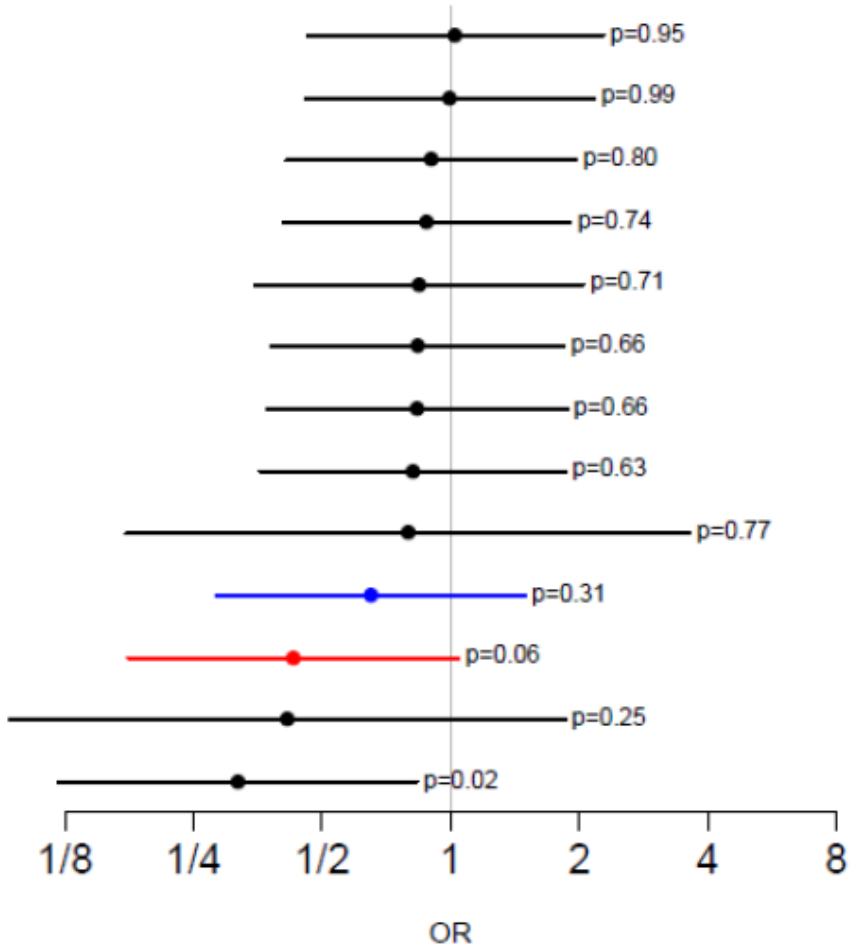
Mulitvariate and Cox

Analysis confirmed independently

80% power to detect a 53% change in HIV infection per 1 sd change in biomark

Use q-test to generate hypotheses for future testing

Estimated odds ratios (high, low, negative) and 95% confidence intervals for V2 assays



IgG V2 A244 K178	Tomaras
IgG Avidity P623−gp70 V1/V2	Alam
Cyclic scrambled crown V2 Biacore	Rao
V2 A244−TH023 ELISA	Berman
biotin V2 peptide 6 sites 169−184	Zolla−Pazner
Cyclic V2 Biacore sites 157−198	Rao
Cyclic V2 scrambled flanks ELISA	Karasavva
Cyclic V2 ELISA sites 157−198	Karasavva
IgA V2 A244 K178	Tomaras
V2 cyclic peptide 42aa	Zolla−Pazner
Scaffolded gp70 V1V2	Zolla−Pazner
V2 MN ELISA	Berman
V2 Hotspot	Montefiori

Correlates Analysis with New Scaffolds

V1V2 Scaffold	OR	P value
gp70V1V2 case A2 (orig. AP)	0.61	0.015
gp70V1V2 case A2 (LL)	0.59	0.008
gp70V1V2_A (GN)	0.68	0.05
gp70V1V2_AE (AP)	0.61	0.013
gp70V1V2_C (GN)	0.55	0.004

Adjusted for IgA effect – Zolla Pazner, Haynes, Liao, Pinter, Nabel

What is IgA doing?

- IgA, as it does in other systems, appears to be interfering with the effect of IgG
- When you look at volunteers with low IgA, other IgG dependent responses such as neutralizing antibody and ADCC are inversely related to infection
- This is not dimeric secretory IgA but monomeric serum IgA
  - Is its presence a function of the gp120 in AIDSVAX B/E? Is it due to alum?
  - Will it be higher with other adjuvants or gp120 proteins?

Tomaras et al., Proc Natl Acad Sci USA 2013; 110:9019-9024

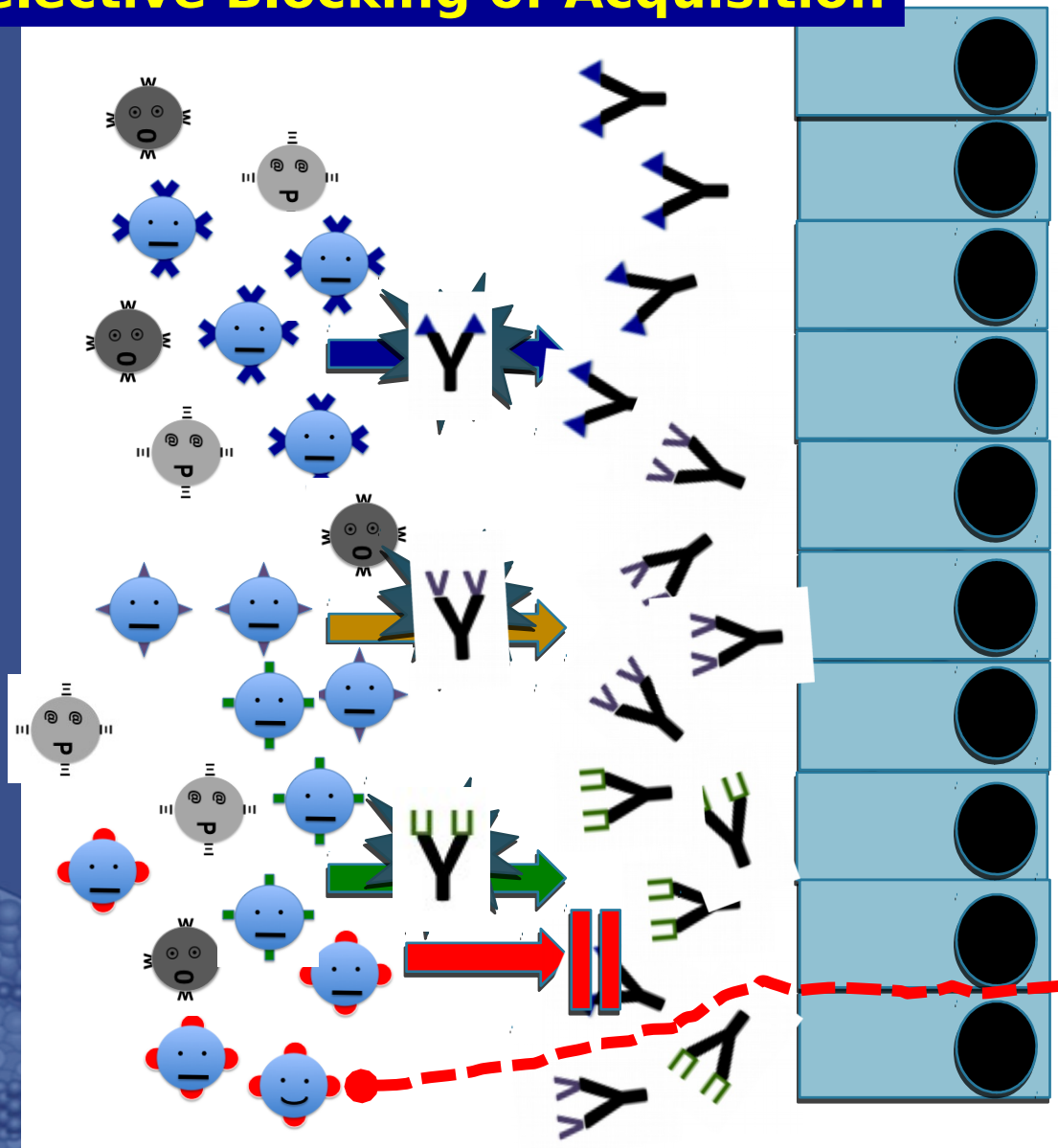
Features of gp120 V2

- Undefined crystal structure, and (as opposed to V1) sharp drop-off in length variation at 40 aa (rarely smaller) => structural partially conserved structure?
- CCR5 binding site (discontinuous epitope includes V1V2)
- a_4b_7 integrin binding site (V2): role in acute infection?
- Over time, **transmitted** viruses increase V2 length and glycosylation (similar in SHIV and maternal-infant transmission)
- Role in quaternary neutralization epitopes (QNEs) of V2V3 (recognized by PG9, PG16, CH01-04)
  - Contributes to Env trimer formation
  - Masking of neutralizing epitopes: V2 length and glycosylation play role in escape from V3 and CD4bs neutralization

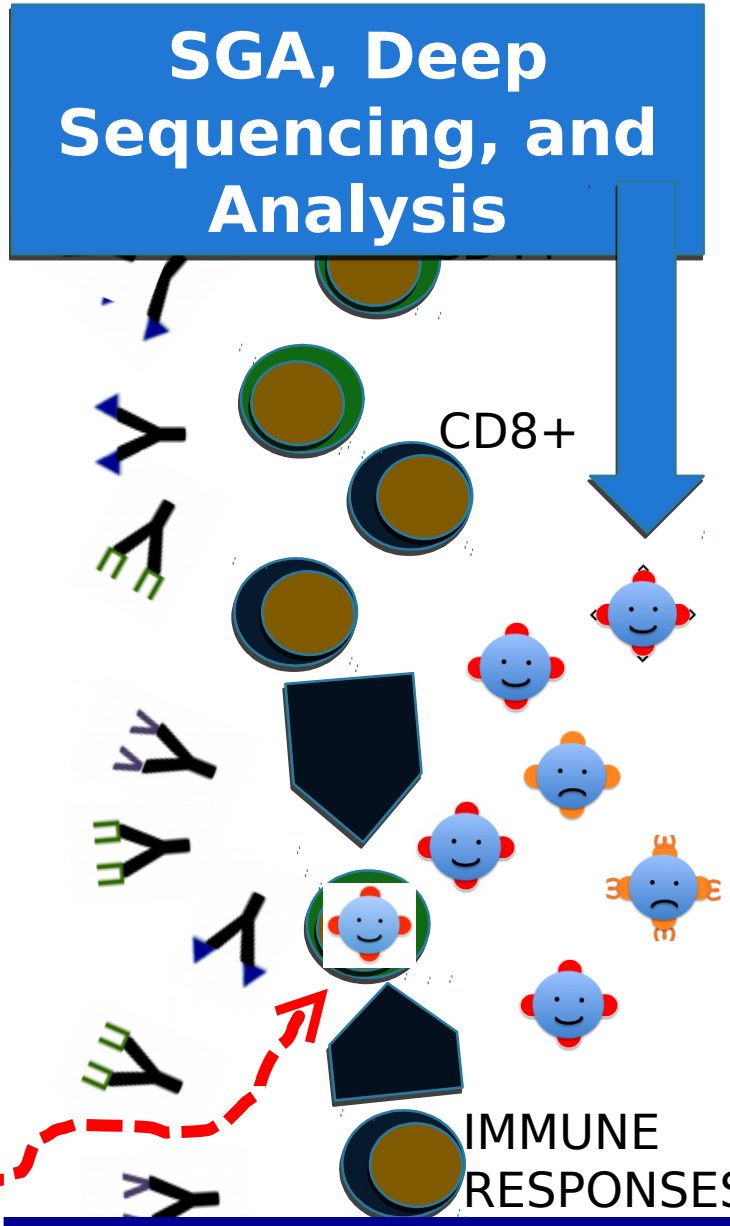
RV144 V2 Sieve Analysis

Rolland et al, Nature 2012

Selective Blocking of Acquisition



SGA, Deep Sequencing, and Analysis



Post acquisition evolution: fitness, recombination, escape

Sieve Analysis of V2

- Comparison of viruses from HIV-1 infected participants in RV144
  - Vaccine/placebo infections vs vaccine insert
  - Viruses from vaccine recipients vs placebo recipients
  - The randomization of vaccine and placebo recipients allows one causally to attribute sequence differences to treatment
- 1025 SGA near-full length sequences done at MHRP and University of Washington
- Analysis – Dr. Morgane Rolland, SCHARP, Dr. Jim Mullins
- Caveat – these are not transmitted/founder viruses the mean time to last negative visit would be ~ 3 months.
- V2 was a major focus of analysis.

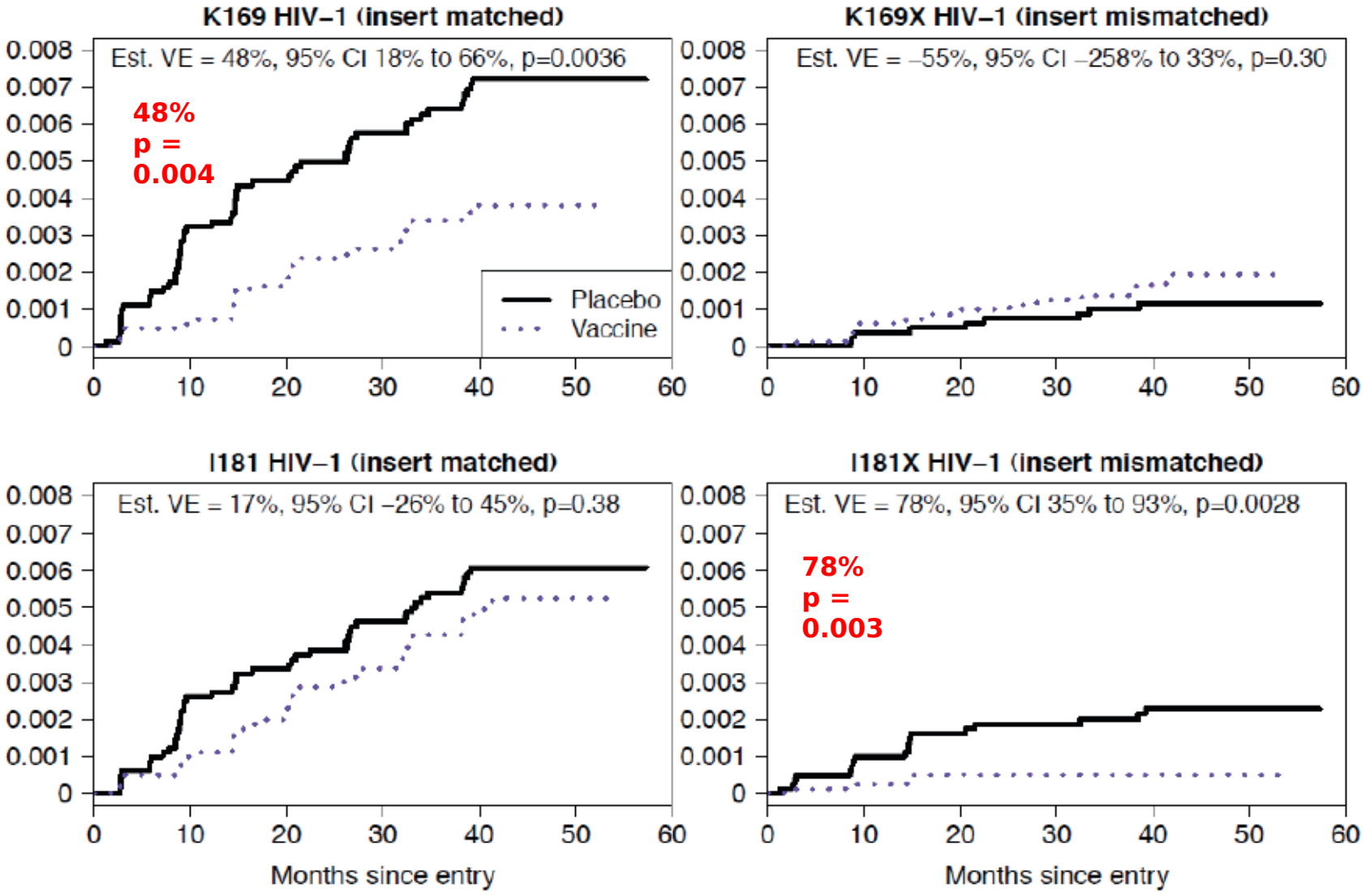
Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V1 and V2

Morgane Rolland[1]*, Paul T. Edlefsen[2]*, Brendan B. Larsen[3], Sodsai Tovanabutra[1], Eric Sanders-Buell[1], Tomer Hertz[2], Allan C. deCamp[2], Chris Carrico[4,5], Sergey Menis[4,5], Craig A. Magaret[2], Hasan Ahmed[2], Michal Juraska[2], Lennie Chen[3], Philip Konopa[3], Snehal Nariya[3], Julia N. Stoddard[3], Kim Wong[3], Hong Zhao[3], Wenjie Deng[3], Brandon S. Maust[3], Meera Bose[1], Shana Howell[1], Adam Bates[1], Michelle Lazzaro[1], Annemarie O'Sullivan[1], Esther Lei[1], Andrea Bradfield[1], Grace Ibitamuno[1], Vatcharain Assawadarachai[6], Robert J. O'Connell[1], Mark S. deSouza[6], Sorachai Nitayaphan[6], Supachai Rerks-Ngarm[7], Merlin L. Robb[1], Jason S. McLellan[8], Ivelin Georgiev[8], Peter D. Kwong[8], Jonathan M. Carlson[9], Nelson L. Michael[1], William R. Schief[4,5], Peter B. Gilbert[2]*, James I. Mullins[3]* & Jerome H. Kim[1]*

nature International weekly journal of science

Phylogenetic tree of env V1/V2 nucleotide sequences with highlights for sequences presenting mutations at either site 169 (in pink) or 181 (in yellow) or at both sites (in grey). Sequences from vaccine recipients are figured in red, those from placebo recipients are in blue.

K169 and I181X mutations are associated with vaccine efficacy



Summary of V3 correlate and sieve effects

- There is a binding antibody “hotspot” CoR to V3 in the linear epitope mapping analysis that includes 307 and 317 in the setting of low IgA.
- Particular genetic sequences in V3 are differentially expressed in vaccine vs placebo breakthrough viruses
- Positions 307 and 317 are on either side of the V3 crown GPGQ sequence.
- Position 307 is canonical (ie, vaccine has efficacy against viruses that match the insert) whereas 317 is non-canonical.

Are there other data that support the idea that there might be a correlate of risk in V3?

Does the V2 correlate tell us about the trials that did not show protection?

Do all vaccines induce antibody to V2?

TRIAL	VACCINE	Anti-V2	Comments
Vax003 - IDU	AIDSVAX B/E gp120	yes	IV drug users
Vax004 - MSM	AIDSVAX B/B	minimal	Antigens cleaved V2
Step/Phambili – MSM (S); hetero (P)	Mrk rAd5 *gag, pol, nef*	No env	
RV144 – low risk hetero	Canarypox vCP1521 + AIDSVAX B/E	yes	VE 31.2%
HVTN 505 - MSM	DNA/rAd5 *gag, pol, nef, env*; subtypes A, B, C	no	

Product Development Strategy:
Increase Vaccine Efficacy from 30% to ≥ 50%

Scientific rationale & feasibility

- Trend of vaccine efficacy (VE) at 12 mos was 60% in RV144
- Additional boost may impact protection level/durability
- Alternative adjuvant may impact magnitude, quality and durability of the immune response

VE 50% would offer a significant public health benefit for regional epidemics

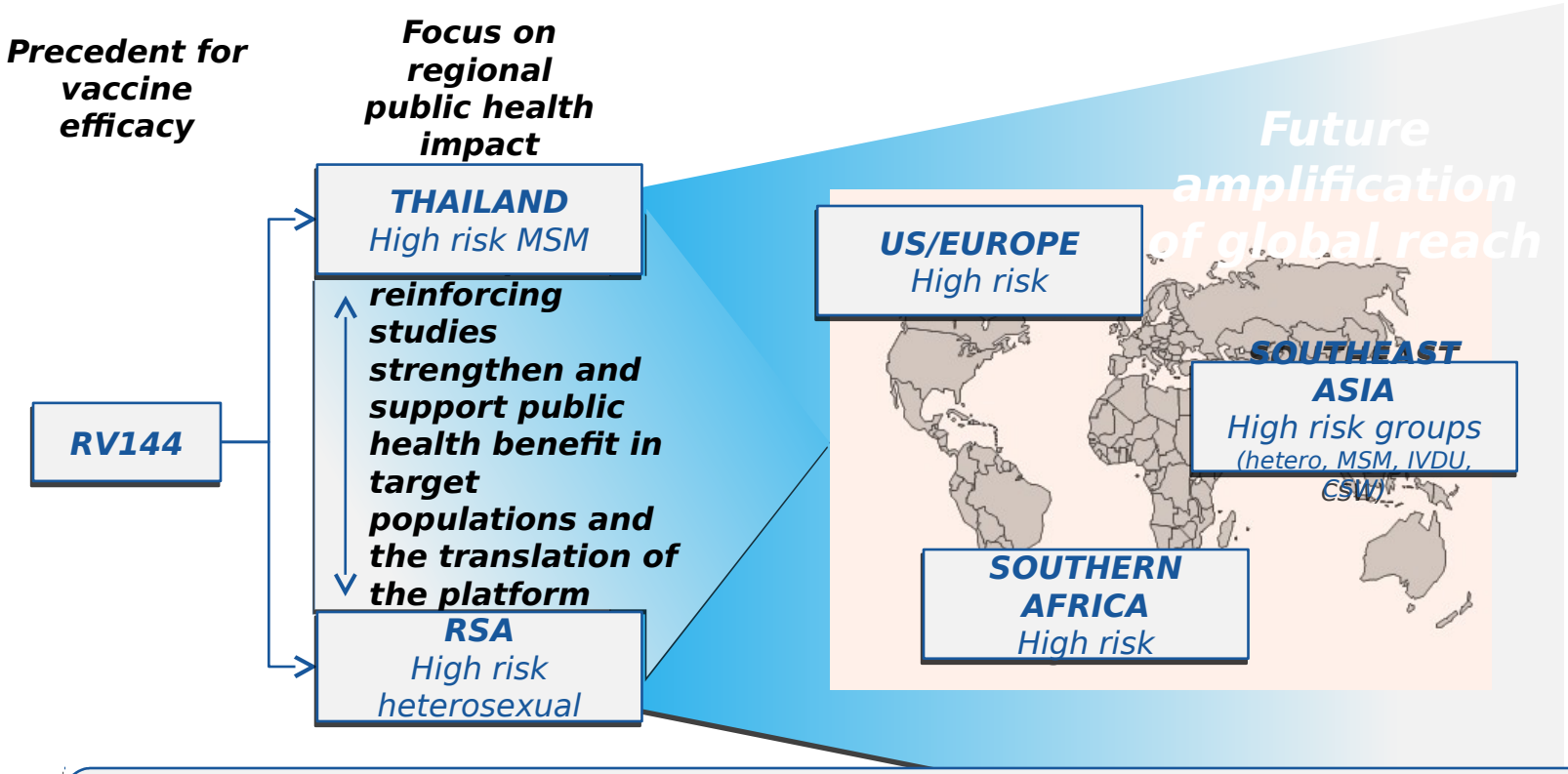
- Thai Ministry of Public Health performed modeling that supports rationale for a 50% effective HIV

The RV144 follow-up trials are furthest along in product development, and offer the timeliest option for an HIV vaccine (P5 Global Strategy)

Summary of Correlates and Sieve Analysis

- Immune correlates (correlates of risk)
  - How did the vaccine work?
  - Are there lab tests that might be associated with the vaccine working to reduce HIV infection?
- In RV144 – yes
    - Antibody against the outer coat (or envelope) protein, specifically the second variable loop was associated with decreased risk of infection
- Other vaccine studies - Vax003, 004, HVTN505 show an interesting and consistent range of V2 responses
- Are the viruses that break through the vaccine different from those that get stopped?
    - Yes – there are scars or markers that suggest that immune responses forced the viruses to change

GLOBAL STRATEGY: Planned studies are interdependent and will amplify global impact and regional relevance.



Global co-ordination of proposed trials provides the strongest regulatory strategy for filing in target markets.

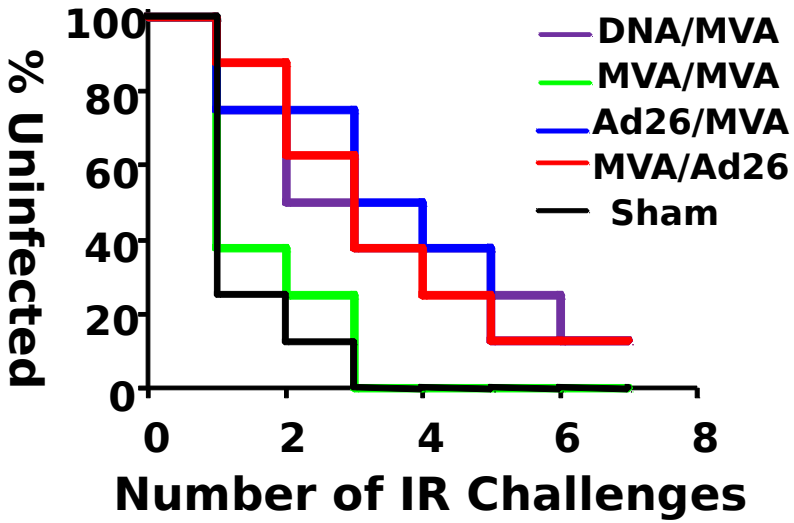
TEST OF CONCEPT (TOC) Phase IIb vs Pivotal Phase III

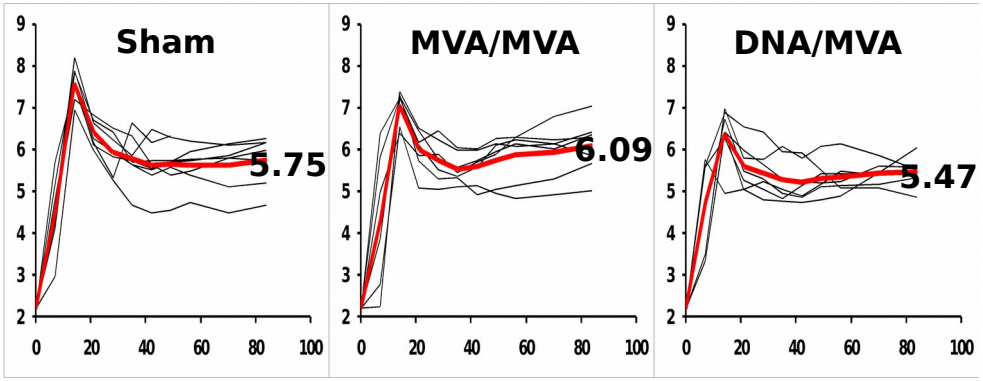
Ad26 – MVA with Mosaic Inserts: A global vaccine?

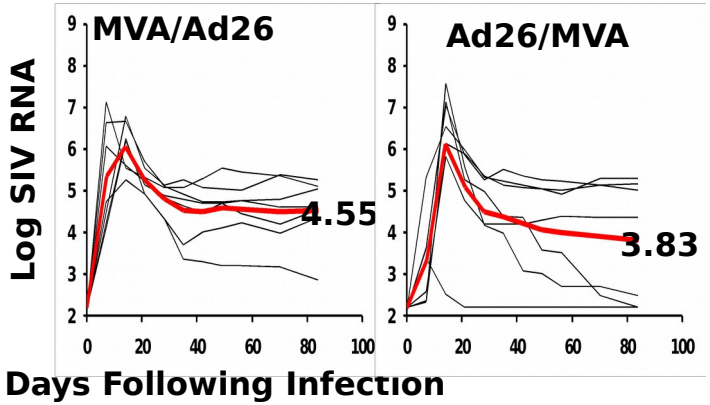
Toshichika, 1884

4 November 2013

Stringent Heterologous SIV Challenge after Ad26-MVA prime-boost Vaccination: Shows Acquisition and VL Benefit







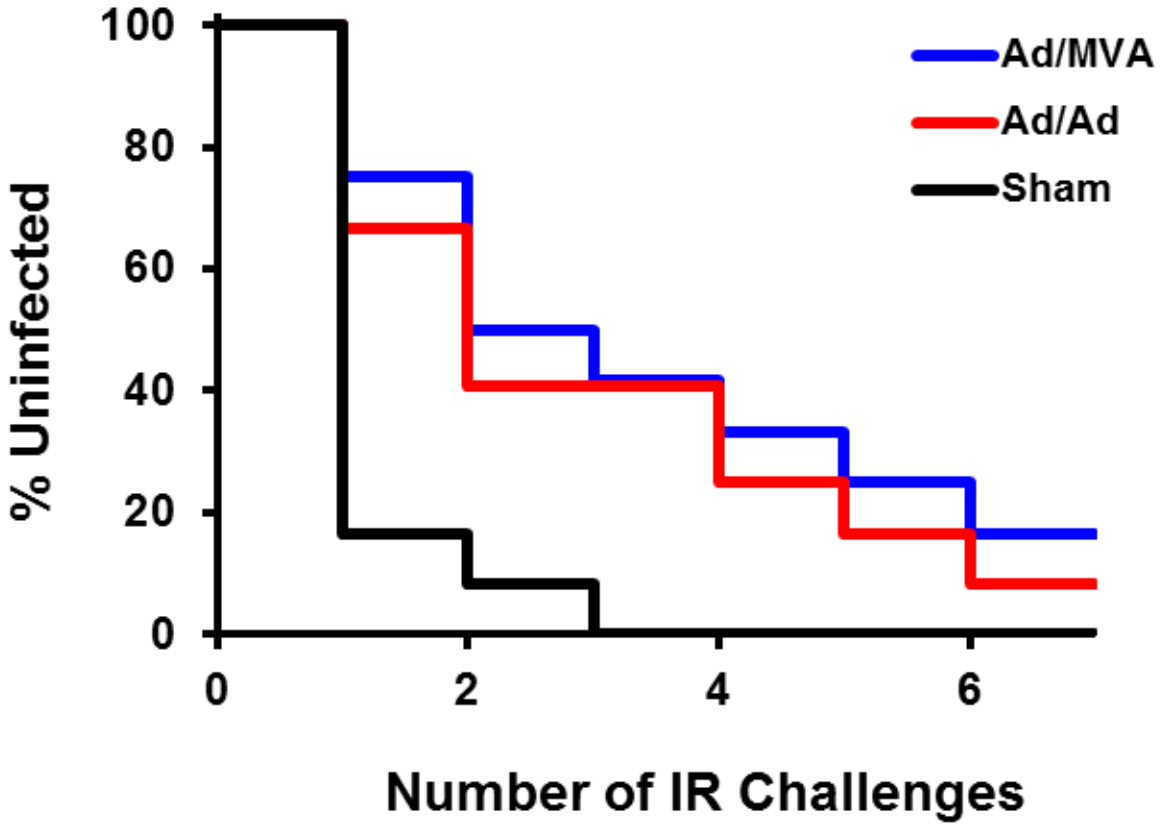
	Challenge # for 50% pos	P-vs Sham *	Hazard Ratio (95% CI)
Sham	1	N/A	1
MVA/MVA	1	0.5587	0.725 (0.247-2.129)
DNA/MVA	2	0.0055	0.186 (0.057-0.611)
MVA/Ad26	3	0.0062	0.198 (0.062-0.632)
Ad26/MVA	3	0.0037	0.174 (0.053-0.567)

Correlates of Risk

- Acquisition endpoint.
  - envelope binding antibody r= .79 p<.0001 (V2 CoR)
  - neutralization antibody r=.50 p=.0034
  - ADCC r=.38 p=.034
- Set point viral load endpoint, Many correlates (N=27);
  - prechallenge gag elispot count and gag elispot breadth were both correlated (r=-.50 p=.006 and r=-.64 p=.0002, respectively) with the endpoint.
  - peak envelope binding antibody r=-.70 followed by prechallenge neutralizing antibodyr=.67.

Ad26-MVA SIV *gag/pol/env* mosaics/SHIV challenge

Findings Support Mosaic Inserts for a Global HIV



Barouch et al, Cell 2013; 155:531

BIDMC, MHRP, LVD/LIR/NIAID

Human Clinical Trials of Ad26-MVA

- Ad26 (subtype A) tested – mosaics made
- MVA (subtype AE) tested – mosaics made
- Human trial of Ad26 – MVA mosaics planned for 2015
- Phase IIb trial anticipated: 2016-2017

The unfulfilled promise of broadly neutralizing antibodies

- A large number of antibodies have now been identified that neutralize a significant proportion of known pseudoviruses
  - 2F5 (gp41)
  - 2G12 (glycosylation)
  - PG9, PG16, PGT121, CH01-04 (V2V3 QNE)
  - VRC01, VRC07, BCN117 (CD4 binding site)
- It has not yet been possible to induce these antibodies using standard immunogens
- Gene therapy?
- RV144 did not induce broadly neutralizing antibodies, measured in current neutralization assays

Early phase trials

Excler JLE et al, Current Opin HIV AIDS, in pre

Vaccine products	HIV-1 subtype	Adjuvant, formulation	Mode and route of administration	References
Subunits				
Lipopeptides	B		IM	[10,11]
Oligomeric gp160	B	DC-Chol	Nasal, vaginal	ANRS VAC14
Trimeric gp140	B′/C	Cerbopol, GLA, Chitosan	Vaginal, IM, IN, oral	[12]
Trimeric gp140	B, C	PCPP, MF59	IM	[13]
Tat protein	C	Alum	SC, ID	[14,15]
Fusion protein Env-Nef-Tat	B	AS02A, AS02V, AS01B	IM	[16,17]
gp41 P1 peptide		Virosomes	IM, IN	[18]
Pox vectors				
ALVAC (vCP1521)	CRF01_AE		IM	[19]
Replicating vaccinia (VV Tiantan)	B′/C		Scarification	[20]
Modified Vaccinia Ankara (MVA)	A, B, C		IM	[21–23]
NYVAC	C		IM	[24]
DNA				
	A, B, C		IM, EP	[25–28]
PENNVAX	B	IL-12, IL-15	IM, EP	[32]
Replication-defective adenovirus vectors				
Ad5	B		IM	[33,34]
Ad35	B, A		IM	[35]
Ad26	A		IM	[36,37]
Adeno-associated virus vector type 2	C		IM	[38–40]
Alphavirus Replicon VEE	C		IM	[41]
Replication-competent Measles Vector	B		IM	Ongoing
Vesicular stomatitis virus vector	B		IM	Ongoing [42]
Prime-boost combinations				
DNA + Trimeric V2-deleted gp140	B	PLG, MF59	IM	[43]
DNA+Env subunit	A, B, C, CRF01-AE	QS-21	ID, IM	[44,45]
DNA+MVA	A, B, C, CRF01_AE, B epitopes	GMCSF	IM, ID, Biojector[a]	[46–56]
DNA+Fowlpox	B		IM	[57,58]
DNA+VV Tiantan	B′/C		Scarification	[20]
DNA+NYVAC	C		IM	[59–61]
Ad5+NYVAC	A, B, C and B		IM	[62]
DNA+Ad5 or Ad35	A, B, C		Biojector[a], IM, ID, SC	[63–68]
DNA IL-12 EP+Ad35-GRIN/ENV	B, A		EP, IM	Ongoing [69]
DNA+MVA+ChAdV63	Conserved sequences		IM	Ongoing, [70]
DNA+VSV	B	IL-12	EP, IM	Ongoing
MVA+Fowlpox	B		IM	[71,72]
Ad35 *env*+Ad26 *env*	A		IM	Ongoing
ALVAC (vCP1521)+AIDSVAX B/E gp120	B, CRF01_AE	Alum	IM	Ongoing
Ad26 *env* A+MVA (natural vs. mosaic)	A, CRF01_AE, mosaic		IM	Ongoing
Ad35-GRIN+adjuvanted fusion protein (non-Env)	A, B		IM	Ongoing
Ad35-GRIN+replicating Sendai	A		IM, IN (Sendai)	Ongoing

Proteins, subunit Env

Pox viruses

DNA

Adenovirus, Ad-associated viruses

Alphavirus, replication comp. Measles

Prime-boost combinations

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